In the present study, a patient with subacute cerebellar degeneration was found to have serum and CSF antibodies that produced immunofluorescence staining of cytoplasmic antigens of cerebellar Purkinje cells, characteristic of type I antibody response. Because the results of a breast examination and mammography were unremarkable, extensive search was undertaken for a pelvic malignant neoplasm. Efforts to detect a tumor culminated, as the patient's clinical condition continued to worsen, in exploratory laparotomy and bilateral oophorectomy. Despite this exhaustive search, the associated tumor, a breast carcinoma, was not detected until more than two years after the onset of the patient's cerebellar deficit. Type I antibody is most frequently associated with gynecologic malignancy, and its reported use as a predictor of occult malignancy has been restricted to carcinoma of the ovary, uterus, and adnexa.[15] An identical antibody response may occur in patients with carcinoma of the breast, however.[3,5] Meticulous follow-up with careful search for an occult tumor should thus be continued in antibody-positive patients in whom a tumor is not found. The possibility of breast as opposed to ovarian, uterine, or adnexal adenocarcinoma should be kept in mind in any patient with type I antibody response. Repeat mammography, in addition to further careful gynecologic evaluation, should be considered in any patient in whom type I antibody is detected but a neoplasm not initially found, with repeat evaluations at three- to six-month intervals over the next year or two.

REFERENCES

1. Brain L, Wilkinson M: Subacute cerebellar degeneration associated with neoplasms. Brain 1965; 88:465-478

2. Henson RA, Urich H: Cortical cerebellar degeneration, *In* Henson RA, Urich H (Eds): Cancer and the Nervous System: The Neurological Manifestations of Systemic Malignant Disease. Oxford, England, Blackwell Scientific Publications, 1982, pp 346-367

3. Anderson NE, Rosenblum MK, Posner JB: Paraneoplastic cerebellar degeneration: Clinical-immunological correlations. Ann Neurol 1988; 24:559-567

4. Greenlee JE, Brashear HR: Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. Ann Neurol 1983; 14:609-613

5. Jaeckle KA, Graus F, Houghton A, Cardon-Cardo C, Nielsen SL, Posner JB: Autoimmune response of patients with paraneoplastic cerebellar degeneration to a Purkinje cell cytoplasmic protein antigen. Ann Neurol 1985; 18:592-600

6. Greenlee JE, Lipton HK: Anticerebellar antibodies in serum and cerebrospinal fluid of a patient with oat cell carcinoma of the lung and paraneoplastic cerebellar degeneration. Ann Neurol 1986; 19:82-85

7. Tanaka K, Yamazaki M, Sato S, Toyoshima I, Yamamoto A, Miyatake T: Antibodies to brain proteins in paraneoplastic cerebellar degeneration. Neurology 1986; 36:1169-1172

8. Greenlee JE, Brashear HR, Herndon RM: Immunoperoxidase labelling of rat brain sections with sera from patients with paraneoplastic cerebellar degeneration and systemic neoplasia. J Neuropathol Exp Neurol 1988; 47:561-571

9. Anderson NE, Rosenblum MK, Graus F, Wiley RG, Posner JB: Autoantibodies in paraneoplastic syndromes associated with small-cell lung cancer. Neurology 1988; 38:1391-1398

10. Smith JL, Finley JC, Lennon VA: Autoantibodies in paraneoplastic cerebellar degeneration bind to cytoplasmic antigens of Purkinje cells in humans, rats and mice and are of multiple immunoglobulin classes. J Neuroimmunol 1988; 18:37-48

11. McLellan R, Currie JL, Royal W, Rosenshein NB: Ovarian carcinoma and paraneoplastic cerebellar degeneration. Obstet Gynecol 1988; 72:922-925

12. Anderson NE, Budde-Steffen C, Wiley RG, et al: A variant of the anti-Purkinje cell antibody in a patient with paraneoplastic cerebellar degeneration. Neurology 1988; 38:1018-1026

13. Tsukamoto T, Yamamoto H, Iwasaki Y, Yoshie O, Terunuma H, Suzuki H: Antineural autoantibodies in patients with paraneoplastic cerebellar degeneration. Arch Neurol 1989; 46:1225-1229

14. Tomimoto H, Brengman JM, Yanigahara T: Paraneoplastic subacute cerebellar degeneration with circulating antibody against neural and extraneural tissues (Abstr). Ann Neurol 1990; 28:247

15. Hetzel DJ, Stanhope CR, O'Neill BP, Lennon VA: Gynecological cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited in metastatic volume. Mayo Clin Proc 1990; 65:1558-1563

16. Moll JWB, Henzen-Logmans SC, Splinter TAW, Van der Berg ME, Vecht CJ: Diagnostic value of anti-neuronal antibodies for paraneoplastic disorders of the nervous system. J Neurol Neurosurg Psychiatr 1990; 53:940-943

17. Hammack JE, Kimmel DW, O'Neill BP, Lennon VA: Paraneoplastic cerebellar degeneration: A clinical comparison of patients with and without Purkinje cell cytoplasmic antibodies. Mayo Clin Proc 1990; 65:1423-1431

18. Cunningham J, Graus F, Anderson N, Posner JB: Partial characterization of the Purkinje cell antigens in paraneoplastic cerebellar degeneration. Neurology 1986; 36:1163-1168

19. Anderson NE, Budde-Steffen C, Rosenblum MK, et al: Opsoclonus, myoclonus, ataxia, and encephalopathy in adults with cancer: A distinct paraneoplastic syndrome. Medicine (Baltimore) 1988; 67:100-109

20. Luque A, Furneaux HM, Wray S, Schold C, et al: Anti-Ri: An autoantibody associated with paraneoplastic opsoclonus. Ann Neurol 1989; 26:178-179

21. Sakai K, Mitchell DJ, Tsukamoto T, Steinman L: Isolation of a complementary DNA clone encoding an autoantigen recognized by an antineuronal cell antibody from a patient with paraneoplastic cerebellar degeneration. Ann Neurol 1990; 28:692-698

22. Furneaux HM, Rosenblum MK, Dalmau J, et al: Selective expression of Purkinje-cell antigens in tumor tissue from patients with paraneoplastic cerebellar degeneration. N Engl J Med 1990; 322:1844-1851

23. Brashear HR, Greenlee JE, Jaeckle KA, Rose JW: Anticerebellar antibodies in neurologically normal patients with ovarian neoplasms. Neurology 1989; 39:1605-1609

24. Furneaux HF, Reich L, Posner JB: Autoantibody synthesis in the central nervous system of patients with paraneoplastic syndromes. Neurology 1990; 40:1085-1091

25. Graus F, Abos J, Roquer J, Mazzara R, Pereira A: Effect of plasmapheresis on serum and CSF autoantibody levels in CNS paraneoplastic syndromes. Neurology 1990; 40:1621-1623

The Papanicolaou Smear

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EVIDENCE IS overwhelming that cytologic screening has been instrumental in effecting a reduction of both incidence and mortality rates of invasive cervical carcinoma.[1-9] The death rate from cervical cancer has decreased by 50% to 70% since the Papanicolaou smear was introduced. Papanicolaou smears are convenient, painless, sensitive, cost-effective, quick, and widely accepted. They are an important part of good care of patients and can help avoid litigation for failure to diagnose cervical cancer.

Limitations of Papanicolaou Smears

Papanicolaou smears are only a portion of a complete pelvic examination. Cervical cytology as a screening test has an incidence of both false-negative and false-positive results.[10-25] These problems will vary with collection technique, the laboratory involved, and patient demographics. Because cervical cytology is a screening test, abnormal findings have to be confirmed histologically.

Suspicious cervical lesions should be evaluated regardless of cytopathologic findings. A biopsy should be taken of gross lesions. Colposcopically directed biopsies are indicated for accurate localization of optimum biopsy sites if an

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obvious lesion is not visible. Doing random cervical biopsies is discouraged. If cytopathologic, colposcopic, and histopathologic findings do not correlate, additional evaluation is indicated.

Techniques for Specimen Collecting

Scraping the transformation zone is the most important step in collecting a Papanicolaou smear. The cervix should be scraped firmly, but care should be taken not to cause bleeding. Slides should not be made too thick. An endocervical specimen is important,[26,27] preferably one obtained by the use of a brush[28,29]; however, a saline-moistened cotton applicator or a "sword" is acceptable.

Careful attention to technique can reduce the incidence of unsatisfactory smears and thus reduce the occurrence of false-negative tests.[25] Less than optimum smears are often the result of the following:

- A thick smear with an abundance of red blood cells or inflammatory cells,
- Poor fixation, often caused by air drying,
- A scarcity of cells caused by wiping the cervix before obtaining the smear specimen,
- Inadequate scraping,
- An absence of endocervical cells,
- Failure to obtain an endocervical specimen.

Inadequate fixation is a problem. Specimens should not be allowed to air dry, so speed is important. Any fixation method used should be approved by the pathologist reading the slide. Thus, communication between clinician and pathologist is important.

Adequacy of Papanicolaou Smear Specimens

The midportion of the menstrual cycle is the optimal time to take a Papanicolaou smear; smears obtained at other times of the cycle, however, are much better than none at all.[25] A menstrual smear is not necessarily an unsatisfactory smear.

A virtually acellular smear is unacceptable and must be repeated. The presence of blood or inflammation affects accuracy. The amount permitted varies with each laboratory. The laboratory *must* report the presence or absence of endocervical cells because the absence of such cells makes uncertain the adequacy of the test.[26]

One slide is considered satisfactory, but two slides are acceptable. Vaginal pool specimens are considered by most to be of limited usefulness.

Reports

Verbal communication between the clinician and pathologist is important. There is no objection to using a Papanicolaou classification system by numbers, but a report is inadequate if no verbal description is given.[30,31]

The degree of inflammation should be reported. Because evaluations will vary from laboratory to laboratory, the clinician must communicate with the pathologist. The treatment of obvious vaginal infection before a smear is done is optimal; a smear must be made if there is any question regarding patient compliance.

A smear should be repeated soon if it is inadequate because of inflammation. If the smear is adequate but there is any inflammation or other benign atypia, it should be repeated in three to six months. Colposcopy is recommended if there are two abnormal smears with benign atypia or inflammation not accounted for by the presence of a specific etiologic agent.

The presence of koilocytes is diagnostic for human papillomavirus infection of the cervix. The cells are characterized by sharply defined perinuclear cavitation bordered by dense, amphophilic cytoplasm. Nuclei show hyperchromasia and may be multiple. Both nuclear changes and perinuclear cavitation must be present.

The presence of endometrial cells should be reported regardless of the age of the patient. Any unusual finding should likewise be reported. As indicated earlier, communication regarding unusual findings is important.

Evaluation of Laboratories

Physicians should consider the following questions before selecting a cytology laboratory[25,32,33]:

- Is the laboratory licensed by the College of American Pathologists? Is it accredited by a volunteer accrediting agency?
- Is there good communication between the cytology laboratory and referring physicians? Does the location of the laboratory encourage such communication? When any new or unsuspected abnormality is found, the physician should be contacted, usually by phone.
- Does the laboratory report unsatisfactory specimens when, for example, there are too few cells for a valid interpretation? The percentage of unsatisfactory specimens will vary with the quality of the submitted specimen.
- Is there documentation of a quality assurance program in the cytology laboratory? Such documentation is required for American College of Pathologists accreditation; thus, an accredited laboratory has a quality assurance program.
- Are adequate staff available to do the work of that laboratory? Are certified cytotechnologists doing the work?

The Human Papillomavirus Epidemic

The human papillomavirus is a factor in the development of carcinoma of the cervix.[34-38] The herpes simplex virus type 2[38] or smoking[39] may likewise be associated.

The prevalence of the human papillomavirus infection varies widely among different population groups. This infection is the most rapidly increasing sexually transmitted disease in this country. Its prevalence is especially high in young adults. Regardless of a person's age, cervical cytologic screening should start when sexual activity begins. The epidemic will get worse before it gets better.

Although 60 types of the human papillomavirus have been identified, not all are related to cancer. Types 16, 18, 31, 33, and 35, among others, have been implicated in both squamous cell carcinoma and adenocarcinoma of the cervix.

A substantial lag time exists between what is seen in women and what is seen in men. Specimens from the sexual partners of female patients with the human papillomavirus infection should be examined using magnification and appropriate staining techniques. Accurate localization of optimum biopsy sites is indicated.

There is concern that characteristics of cervical cancer may be changing, with some lesions progressing rapidly.[40] This is possibly related to the type of associated human papillomavirus. There is evidence that the prognosis is influenced by the human papillomavirus type.[40]

Guidelines

Papanicolaou smears should be done annually after a woman becomes sexually active or reaches the age of 18 years.[41-43] There is no age limit above which annual Papanicolaou smears are not recommended.[23,41] The following reasons are given for these recommendations:

- The annual physical examination has proved a crucial, highly effective preventive measure.
- The increased diagnostic yield of annual Papanicolaou smear screening is cost-effective because everyone needs an examination anyway.
- The Papanicolaou smear is an easy, inexpensive, and painless test to do.
- The human papillomavirus epidemic is a problem of enormous magnitude.
- The screening frequency compensates for a lack of patient compliance.
- Annual screening should increase persons' compliance in other areas of health care screening.

High-risk persons may require screening more often than annually. These include women who began their sexual activity early, women with multiple sexual partners, patients with a history of any lower genital tract infection of any disease related to the human papillomavirus, those with sexual partners who have had any disease related to the human papillomavirus, and women who had exposure to diethylstilbestrol in utero.

REFERENCES

1. Periodic Cancer Screening for Women (ACOG Statement of Policy). Washington, DC, American College of Obstetricians and Gynecologists, 1980
2. Jordan MJ: Has the survival rate from invasive carcinoma of the cervix been influenced by cytology screening? Mod Med 1971; 18:180-188
3. Walton RJ: The task force on cervical cancer screening programs (Editorial). Can Med Assoc J 1976; 114:981
4. Christopherson WM, Lundin FE Jr, Mendez WM, Parker JE: Cervical cancer control: A study of morbidity and mortality trends over a 21-year period. Cancer 1976; 38:1357-1366
5. Johannesson G, Geirsson G, Day N: The effect of mass screening in Iceland, 1965-1974, on the incidence and mortality of cervical carcinoma. Int J Cancer 1978; 21:418-425
6. Cramer DW: The role of cervical cytology in the declining morbidity and mortality of cervix cancer. Cancer 1974; 34:2018-2027
7. Timonen S, Nieminen U, Kauraniemi T: Cervical screening (Letter). Lancet 1974; 1:401-402
8. Dickinson LE: Control of cancer of the uterine cervix by cytologic screening. Gynecol Oncol 1975; 3:1-9
9. Devesa SS, Silverman DT, Young JL Jr, et al: Cancer incidence and mortality trends among whites in the United States, 1947-1984. J Natl Cancer Inst 1987; 79:701-770
10. Coppleson LW, Brown B: Estimation of the screening error rate from the observed detection rates in repeated cervical cytology. Am J Obstet Gynecol 1974; 119:953-958
11. Frost JK: Diagnostic accuracy of cervical smears. Obstet Gynecol Surv 1969; 24(Pt 2):892-908
12. Gray LA: The frequency of taking cervical smears. Obstet Gynecol Surv 1969; 24(Pt 2):909-913
13. Koss LG: Dysplasia: A real concept or a misnomer? Obstet Gynecol 1978; 51:374-379
14. Shulman JJ, Hontz A, Sedlis A, Walters AT, Balin H, LoSciuto L: The Pap smear: Take two. Am J Obstet Gynecol 1975; 121:1024-1028
15. Richart RM: The patient with an abnormal Pap smear: Screening techniques and management. N Engl J Med 1980; 302:332-334
16. Berkowitz RS, Ehrmann RL, Lavizzo-Mourey R, Knapp RC: Invasive cervical carcinoma in young women. Gynecol Oncol 1979; 8:311-316
17. Martin PL: How preventable is invasive cervical cancer? A community study of preventable factors. Am J Obstet Gynecol 1972; 113:541-548
18. Rylander E: Negative smears in women developing invasive cervical cancer. Acta Obstet Gynecol Scand 1977; 56:115-118
19. International Agency for Research on Cancer: Screening for squamous cervical cancer: Duration of low risk after negative results of cervical cytology and its implication for screening policies. Br Med J 1986; 293:659-663
20. Roberts AD, Denholm RB, Cordiner JW: Cervical intraepithelial neoplasia in postmenopausal women with negative cervical cytology. Br Med J [Clin Res] 1985; 290:281
21. Weintraub NT, Violi E, Freedman ML: Cervical cancer screening in women aged 65 and over. J Am Geriatr Soc 1987; 35:870-875
22. Mandelblatt J, Gopaul I, Wistreich M: Gynecological care of elderly women—Another look at Papanicolaou smear testing. JAMA 1986; 256:367-371
23. Fletcher A: Screening for cancer of the cervix in elderly women. Lancet 1990; 335:97-99
24. Koss LG: The Papanicolaou test for cervical cancer detection—A triumph and a tragedy. JAMA 1989; 261:737-743
25. Improving the Quality of Clinician Pap Smear Techniques and Management, Client Pap Smear Education, and the Evaluation of Pap Smear Laboratory Testing: A Resource Guide for Title X Family Planning Projects. Washington, DC, US Dept of Health and Human Services, 1989
26. Elias A, Linthorst G, Bekker B, Vooijs PG: The significance of endocervical cells in the diagnosis of cervical epithelial changes. Acta Cytol (Baltimore) 1983; 27:225-229
27. Killough BW, Clark AH, Garvin JB: Correlation between cytodiagnosis and the presence of endocervical or squamous metaplastic cells in gynecologic smears. Acta Cytol (Baltimore) 1988; 32:758-761
28. Alons-van Kordelaar JJM, Boon ME: Diagnostic accuracy of squamous cervical lesions studied in spatula-cytobrush smears. Acta Cytol (Baltimore) 1988; 32:801-804
29. Reissman SE: Comparison of two Papanicolaou smear techniques in a family practice setting. J Fam Pract 1989; 26:525-527
30. National Cancer Institute Workshop: The 1988 Bethesda system for reporting cervical/vaginal cytologic diagnosis. JAMA 1989; 262:931-934
31. The 1988 Bethesda system for reporting cervical/vaginal cytologic diagnosis, Reprod Med 1989; 34:779-785
32. AMA Council on Scientific Affairs: Quality assurance in cervical cytology. JAMA 1989; 262:1672-1679
33. Quality Pap Tests: A Position Paper. Skokie, Ill, College of American Pathologists, 1988
34. Reeves WC, Brinton L, Garcia M, et al: Human papillomavirus infection and cervical cancer in Latin America. N Engl J Med 1989; 320:1437-1441
35. Lorincz AT, Temple GF, Kurman RJ, Jenson AB, Lancaster WD: Oncogenic association of specific human papillomavirus types with cervical neoplasia. J Natl Cancer Inst 1987; 79:671-677
36. Gupta JW, Saito K, Saito A, Fu Y, Shah KV: Human papillomavirus and the pathogenesis of cervical neoplasia. Cancer 1989; 64:2104-2110
37. Werness BA, Levine AJ, Howley PM: Association of human papillomavirus types 16 and 18 E6 proteins with p53. Science 1990; 248:76-79
38. Kurman RJ: Is human papillomavirus a primary factor in the causation of cervical neoplasia? Does herpes simplex virus play a subordinate role? J Gynecol Surg 1989; 5:225-227
39. Slattery ML, Robinson LM, Schuman KL, et al: Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. JAMA 1989; 261:1593-1598
40. Walker J, Bloss JD, Liao S, Berman M, Bergen S, Wilczynski SP: Human papillomavirus genotype as a prognostic indicator in carcinoma of the uterine cervix. Obstet Gynecol 1989; 74:781-785
41. Report of Task Force on Routine Cancer Screening—ACOG Committee Opinion #68. Washington, DC, American College of Obstetricians and Gynecologists, 1989
42. Bearman DM, MacMillan JP, Creasman WT: Papanicolaou smear history of patients developing cervical cancer: An assessment of screening protocols. Obstet Gynecol 1987; 69:151-155
43. Shy K, Chu J, Mandelson M, Greer B, Figge D: Papanicolaou smear screening interval and risk of cervical cancer. Obstet Gynecol 1989; 74:838-843